REMARKS

Claims 1-4, 7-11 and 28-46 are currently pending. Claim 1 has been amended. Claims 15-21 have been cancelled. Claim 1 has been amended to incorporate the specific salmeterol acid addition salts as supported throughout and specifically on page 3, fourth full paragraph of the specification. No new matter has been introduced into the application by way of amendment.

Objection to the Specification:

The examiner has objected to the specification for example page 13, lines 34-36 to a the incorporation of foreign application or patent, or to a publication, i.e. WO 97/12687 as being improper. While not agreeing with the propriety of the Examiner's objection and solely to advance prosecution, Applicants have inserted the US Patent equivalents of the cited publication (which is in conformity with the rules governing incorporation by reference) and no new matter has been inserted into the application by way of amendment.

Double Patenting:

(a) Claims 1-4, 7-12, 15-21 and 28-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of US. Patent No. 6,630,466. The attached terminal disclaimer should be sufficient to obviate the aforementioned rejection. Withdrawal of the rejection is respectfully requested.

(b) Claims 1-4, 7-12, 15-21 and 28-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-14 of US. Patent No. 6,680,345. The attached terminal disclaimer should be sufficient to obviate the aforementioned rejection. Withdrawal of the rejection is respectfully requested.

(c) Claims 1-4, 7-12, 15-21 and 28-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-23 of US. Patent No. 6,919,325. The attached terminal disclaimer should be sufficient to obviate the aforementioned rejection. Withdrawal of the rejection is respectfully requested.

(d) Claims 1-4, 7-12, 15-21 and 28-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of US. Application No. 10/736,264.

MPEP 804(I)(B) states:

"If the "provisional" double patenting rejections in both applications are the only rejections remaining in those applications, the examiner should then withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent. The examiner should maintain the double patenting rejection in the other application as a "provisional" double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent."

Once the instant response is reviewed by the Examiner and the Examiner determines that the only rejection remaining in the instant application is the aforementioned provisional double patenting rejection, the Examiner should withdraw the rejection in the instant application and permit the application to issue as a patent. The examiner should then maintain the double patenting rejection in the other application as provisional which will be converted into a double patenting rejection when the instant application issues as a patent.

Rejection under 35 USC 103(a):

(a) Rejection of claims 1-4, 7-12 and 15-21 as being unpatentable over Freund et al in view of Hochrainer, et al and Wolf, et al. This rejection is respectfully traversed.

The Examiner contends that although the prior art references differ from the instant claims in that the prior art does not 1) expressly disclose the effective amounts of tiotropium bromide and salmeterol in the composition herein to be administered and 2) expressly disclose the compositions therein contained in single preparation or two separate preparations, however, it would have been prima facie obvious to employ the particular combination composition of tiotropium bromide and salmeterol, and to optimize the effective amounts of active agents in the composition herein to be administered, and to store the combination in a single or two separate containers because tiotropium and salmeterol respectively are old and well known to be used in treating COPD and asthma and optimization of the known amounts of the known active agents to be administered is considered within the skill of [the] artisan. *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. Further, a single or two separate containers is deemed obvious since they are all within the knowledge and conventional skills of [a] pharmacologist to conveniently assist the user and prescriber for easy dispensary of the medication.

The Examiner has failed to establish a prima facie case of obviousness. The court states in *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987) that "[o]bviousness

cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)."

The Examiner's argument has employed improper hindsight analysis and clearly ignored the intended teaching of Freund et al.

Applicants may argue that the examiner's conclusion of obviousness is based on improper hindsight reasoning. However, "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and ***does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.***" In re McLaughlin 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).

Freund et al is directed to propellent free formulations comprising at least one steroid. The Examiner emphasizes that Freund formulations comprise acids and refers to col 2, lines 60-64. It is clearly stated in the paragraph preceding this quotation that acids surprisingly improve the stability of the **steroid**-containing preparations. Freund discloses about 80 steroids. In addition to these Freund mentions 16 betamimetics, 4 anticholinergics , a few antiallergics and some PAF - antagonists. Tiotropium is mentioned as one of the possible anticholinergics, salmeterol is listed in the betamimetics group. The Examiner admits that Freund et al fails to specifically teach a combination of tiotropium with salmeterol as being of particular utility. To mitigate this difference, the Examiner combines Freund et al with Hochrainer et al. However, Freund et al and Hochrainer et al (DE 198 47 970) disclose the same active ingredients. In this respect Hochrainer does not add anything to Freund et al. In other terms, if Freund et al is not a teaching of the specific combination of tiotropium with salmeterol, Hochrainer et al is not a mitigating reference.

The Examiner's assessment that Hochrainer teaches salmeterol and tiotropium as old and well known is not supported. Salmeterol is mentioned in Hochrainer et al once (page 3, line 30). Tiotropium is mentioned twice (page 3 line 21 and page 4, line 40). From this mere mention of the two active ingredients it cannot be concluded that Hochrainer would tech them to be "old and well known". Neither Freund et al nor Hochrainer et al, taken alone or in combination, deliver any motivation or even a mere hint of suggestion to the skilled artisan to

specifically focus on a propellent free solution formulation comprising the specific combination of tiotropium with salmeterol.

Wolf et al merely teaches salmeterol (not tiotropium) and formulations thereof. The formulations mentioned by Wolf are either MDI- or powder-formulations. MDI-formulations are propellent containing. As the instant invention is clearly directed to propellent free solution formulations of salmeterol and tiotropium containing combinations, Wolf is of no relevance to the instant case.

With regard to the Walland declaration, the Examiner's arguments are inconsistent and scientifically illogical. The Examiner argues that the cited references render the instanly claimed combination of tiotropium salts with specific salmeterol salts obvious even though none of the cited references disclose more than "salmeterol" per se (i.e., without mention of any salts thereof). Whereas the Examiner considers the mere mention of "salmeterol" alone in the prior art references to be sufficient to render obvious specifically claimed salts of salmeterol. The Examiner's arguments are inconsistent and apply an inconsistent standard, i.e., indicating a preference of the teachings of the prior art versus the teachings of the Walland declaration and the merits of the invention as instantly claimed.

Further, the Examiner argues that that tiotropium brmide and salmeterol hemisulfate were only tested with doses of 3 μg tiotropium bromide and 6 or 12 μg salmeterol hemisulfate. This argument implies that the instantly filed claims would only be allowable if each and every salt was subjected to the testing conditions outlined by Walland, preferably also with different doses. This is scientifically illogical as the activity of the compounds according to the invention is provided by the active principles, i.e., tiotropium (the cation) and salmeterol. The skilled artisan would not have expected that the surprising over additive effects and the reduced side effects described in the Walland declaration would be significantly influenced if either the counterion to tiotropium was changed from bromide to another anion or if the salt form of salmeterol were to be modified.

Therefore, Applicants believe that the Examiner has failed to present a prima facie case of obviousness and withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, Applicants respectfully submit that this application is now in condition for allowance and earnestly request such action.

If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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